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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,301	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on August 1, 2006.

Preliminary Remark

Claim 4 is canceled.

Claims 1-3 and 5-8 are pending and are under prosecution herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The new matter rejection of claims 1-3 and 5-8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on April 18, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 1, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

MPEP 2163(I) states "[t]he issue raised in the cases is most often phrased as whether the original application provides "adequate support" for the claims at issue or whether the material added to the specification incorporates "new matter" in violation of 35 U.S.C. 132."

MPEP 2163.07 gives some guidance in when an amendment does not introduce new matter:

(I) Rephrasing: mere rephrasing of a passage does not constitute new matter;

(II) Obvious errors: an amendment to correct an obvious error does not constitute new matter;

(III) Inherent Function, Theory, or Advantage: *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill";

It is clear that the claim amendment drawn to a method which employs a range of amount of genomic DNA (the range of which being 10-40 ng) per 100 sites, wherein the method results in at least 98% of single nucleotide polymorphisms are detected does not qualify under "rephrasing," "obvious errors," or "inherent function."

One of skill in the art, in determining whether applicants had contemplated the invention as embraced by the claim amendment, must determine the full-breadth the claim now embraces.

The full breadth of the claims embraced by the claims are drawn to a method which simultaneously amplifies as little as two SNP sites to a plurality of SNP sites (100, 10,000, 100,000 sites), wherein the amount of genomic DNA employed for amplification is 10-40 ng per 100 sites. The amplified products are then typed by an assay, which results in 98% of single nucleotide polymorphisms.

Of course, for at least 98% of the SNPs to be detected, at least 98% of the SNPs must be amplified, simultaneously.

Applicants rely on a single description wherein 40 ng of starting DNA (page 15, second paragraph) is employed for simultaneously amplifying 100 target sites (page 15, 3rd paragraph), followed by the Invader assay typing for single nucleotide polymorphisms in the resulting amplicons

(page 18, 1st paragraph), which resulted the detection of fluorescence in 98% of SNPs (page 19, 1st paragraph).

One of skill in the art would clearly recognize that at some point, the ability to simultaneously amplify a plurality of SNP sites, the plurality being much greater than 100 sites (as the claims do not have an upper limit) would fail, clearly, with the ability to amplify at least 98% of the SNP sites.

Thus, one of skill in the art would not recognize that Applicants were in possession of the full-breadth of the instantly claimed invention based on a single example of amplifying 100 sites using 40 ng of genomic DNA, wherein at least 98 of the sites were amplified and detected.

It should be noted that *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973), the court also expressed that when determining new matter, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

As one of skill in the art would be not able to find any support that the full breadth of the claimed method would result in amplification of at least 98% of all SNP sites targeted, the support for the newly introduced limitation would appear to be based on an assumption, to which the court held insufficient.

Response to Arguments:

For the record, the rejection of record is a New Matter rejection.

Claim construction:

Independent claim 1 conducts two steps (independent claim 5 fails analogously):

a) simultaneously amplifying at least two sites of SNPs using 10-40 ng of DNA per 100 sites; and

b) typing the amplified products in an INVADER or TAQMAN assay,

wherein the result that at least 98% of SNPs are detected.

The phrase, "the result that at least 98% of SNPs are detected," necessarily embrace the embodiment, wherein using 10 ng of DNA to simultaneously amplify 100 SNP sites results in the successful amplification of at least 98 SNP sites.

Claims prior to the rejection did not have the limitation imposed by the phrase, "with the result that at least 98% of single nucleotide polymorphisms are detected."

The issue at hand is whether or not Applicants' were in possession of a method that amplifies 100 SNP sites employing a range of 10-40 ng of DNA, which results in the, newly introduced limitation of, "at least 98%" SNP sites being successfully amplified (98 SNPs).

Response to Arguments:

In introducing this limitation, Applicants relied on a single example provided in the specification which employed a specific amount of DNA, that is 40 nanograms of DNA for simultaneously amplifying 100 SNP sites. (see page 15, instant specification), for the support of the amendment.

The specification provided for a method which simultaneously amplifies 100 single nucleotide polymorphisms using the most upper limit of **40 nanograms** of DNA, wherein the amplification results in 98 of the SNP sites (hence, 98%) being amplified.

The specification, however, failed to provide support for the full breadth of the method, which is drawn to a method which simultaneously amplifies 100 single nucleotide polymorphisms

using 10 nanograms of DNA, wherein the amplification results in 98% of the polymorphisms being amplified.

Applicants contend that the specification provides an example of 98 of 100 SNP sites being successfully typed using 40 ng of input DNA (see page 4, bottom paragraph, Response). Applicants also contend that the specification also provides an example (Example 4) in which a single site is typed using only 0.1 ng of DNA template, and this example also explains that the multiplexed example (Example 3) may therefore be performed using as little as ¼ the amount (i.e., 10 ng per 100 SNP sites) used in Example 3 (page 4, bottom through page 5, 1st paragraph).

Applicants' arguments are not found persuasive because the claims do not recite what Applicants' are contending.

Claim recites that a plurality of nucleotide sequences comprising at least two sites of SNP is simultaneously amplified using 10-40 ng per 100 sites.

Claim **does not** recite that 10-40 ng per 100 SNP sites is used in an INVADER assay or TAQMAN PCR method.

In addition, while it is uncertain just exactly what type of INVADER assay Applicants are referring to, but to Examiner's knowledge, INVADER assay employs a set of primers which generate a flap structure, wherein the cleavage of the flap (whose structure does not comprise any of the target sequences) results in the detection of the presence of target nucleic acids (see various patents issued to ThirdWave Technology). The method does not rely on the amplification of actual target sequences, but a proliferation of arbitrary sequence that is cleaved (flap structure).

While TaqMan® PCR assay does rely on amplification, the specification does not provide any support that a multiplex TaqMan® was performed using 10 ng of DNA to simultaneously type 100 SNP sites.

The fact that the claims require that at least 98% of SNPs are detected necessarily require that at least 98 SNP sites are successfully amplified using 10 ng of DNA in a simultaneously amplification.

The specification does not have any support for this limitation, and thus the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 3, 5, and 7 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082), made in the Office Action mailed on April 18, 2006 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 10, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

Preliminarily, the full-breadth of the claims are construed as follows.

The limitation imposed by the phrase, "genomic DNA whose amount is 10-40 ng per 100 sites," embodies a range of 0.1 ng to 0.4 ng per a single SNP site. Thus, the method requires at least 0.2 ng of genomic DNA in claims 1 and 3 which recite the step of simultaneously amplifying "at

least two sites," and at least 0.1 ng of genomic DNA in claims 5-8 which recite the step of simultaneously amplifying one or more sites."

Additionally, claims 7 and 8 does not require that the 50 pairs of more primer be primer pairs which amplifies different SNP sites. Thus, employing at least 50 pairs of the primer pairs which amplify a single SNP site (i.e., having the same sequences) would necessary meet this limitation.

While Applicants' arguments are moot in view of this new ground of rejection, to the extent applicable, the arguments will be addressed in the, "Response to Arguments" section.

Mein et al. disclose a method of coupling multiplex amplification of polymorphic loci from a genomic DNA, followed by detecting the single nucleotide polymorphisms by Invader® assay method (Abstract, page 331, 2nd column).

Mein et al. disclose that 36 SNPs sites were amplified (page 331, 2nd column), employing 10 ng of starting DNA. Mein et al. are silent as to how many SNP sites were simultaneously amplified using the 10 ng of starting DNA.

Hence, Mein et al. do not employ 50 or more primer pairs in their method nor genomic DNA whose amount is 10-40 ng per 100 sites.

Wang et al. disclose a method of detecting SNPs by first simultaneoutly amplifying (or multiplexing) a plurality of primer pairs, including 558 loci, necessarily including more than 50 primer sets, considering that a singe primer set amplifies a single loci (page 1080, 3rd column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Mein et al. with the teachings Wang et al. to arrived at the claimed invention for the following reasons.

The motivation to multiplex more target sites in amplification, that is, simultaneously amplifying multiple target sites, is a well-established desire in the art. As Wang et al. put it:

> "We next sought to **decrease substantially the sample preparation required to generate large numbers of SNPs, as required to perform a genome scan. We developed a protocol based on multiplex PCR in which primer pairs from many different loci are combined in a single reaction**." (page 1080, 3rd paragraph, 1st paragraph)

Wang et al. employ 100 ng of DNA for simultaneously amplifying a plurality of loci, including 24 sets of approximately 23 loci, 12 sets of approximately 46 loci, 6 sets of approximately 92 loci (page 1080, 3rd paragraph, 1st paragraph), and a single set of 558 loci.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. with the teachings of Wang et al. to arrive at simultaneously amplification involving at least 50 pairs of primers or more.

Wang et al. disclose that 12 sets of 46 loci; (46 loci being amplified simultaneously); 6 sets of 92 loci; a single set of 558 loci were amplified simultaneously (page 1080, 3rd column).

While the artisans disclose that different multiplex amplification reactions gave different percentage of loci being successfully amplified, Wang et al. explicitly discusses that it may be possible to salvage the unsuccessful assays by grouping them into additional multiplex sets or by *redesigning* the assays.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. and the teachings of Wang et al. to achieve multiplex amplification involving a plurality of primers for the advantage of decreasing sample preparation (as expressed by Wang et al.), wherein the artisan would have had a reasonable

expectation of success at such combination as Wang et al. clearly envisions that by redesigning, multiplexing even up to 558 loci would be achievable, through optimization.

Regarding optimization, the MPEP 2144.05(II)(A) clear that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995). Analogously, optimizing parameters for multiplexing multiple target sites in an amplification reaction would be considered routine, as provided for by Wang et al.

In addition, based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in a 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci), with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants contend that the combination of references do not disclose or suggest all of the features of the claims in that the Office provides no reference describing use of an amount of template of about 0.1 ng per SNP site. Applicants argue that the Office does not explain any motivation why such a small amount of DNA template should be used (page 5, 5th paragraph, Response).

Applicants are advised that the claims are not limited to 0.1 ng per SNP site, but rather cover a range with an upper limit of 0.4 ng per SNP site.

In addition, Applicants' argument that one of ordinary skill in the art would not recognize the need to minimize the amount of sample required in an assay is not found persuasive. The whole discipline of PCR is based on the recognition of such a need. The art is prolific with the desire to amplify nucleic acids from sample whose source is limited (i.e., amplification from a single cell, sample from a deceased individual, etc.). Thus, to state that one of ordinary skill in the art at the time the invention was made would not have recognized the need to improve in the amount of starting amount DNA required in an amplification method is simply not persuasive.

In addition, in amplifying 558 SNP sites using a starting amount of 100 ng of DNA, resulted in the use of 0.18 ng of DNA per SNP site.

Since half of the SNP sites (50%) were successfully amplified, this would have meant that 279 SNP sites were successfully amplified with a 100 ng of DNA.

This would also mean that 279 SNP sites were 100% amplified using 100 ng of DNA.

This would mean that 0.35 ng of DNA per single SNP is employed, which would further mean that 35 ng per 100 SNPs were amplified.

Since Wang et al. demonstrate that 35 ng DNA resulted in 100% of 100 SNP sites being amplified, the art clearly teaches the limitation of using 10-40 ng of DNA per 100 SNP sites.

One of ordinary skill in the art at the time the invention was made would have clearly expected that 279 SNP sites would have 100% amplified with 100 ng of DNA, which translates to 35 ng of DNA per 100 SNP sites.

Applicants' arguments are moot in view of this fact and thus, the rejection is maintained.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

The rejection of claims 2, 6, and 8 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082) as applied to claims 1, 3, 5, and 7 above, and further in view of Brooks (US 2001/0046670 A1, issued November 29, 2001, priority October 7, 1999), made in the Office Action mailed on April 18, 2006 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 10, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

The teachings of Mein et al. and Wang et al. have already been discussed above.

Neither Mein et al. nor Wang et al. employ "hot start" amplification (claims 2, 6, and 8)

Brook discloses a multiplex amplification [0076] reaction which involves hot start amplification [0066].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mein et al., and Wang et al. with the advantage offered by Brooks to arrive at the invention as claimed for the following reasons.

Brook clearly discusses the advantage of employing "hot start" PCR method:

"...other 'Hot Start' type PCR conditions are used to limit primer dimer artifacts as much as possible." [0066].

As one of ordinary skill in the art in the art of amplification would recognize that primer dimer artifacts are to be minimized in amplification procedures, it would have been obvious to implement this teachings into the teachings of Mein et al., and Wang et al. to arrive at the claimed invention with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants do not present any new arguments than those which were fully addressed above.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicants' statement regarding an Interview is acknowledged.

Submission of PTO-713A is suggested prior to the interview, with issues to be discussed and claim amendment (if any) should be presented in a facsimile transmission.

Interviews after final rejection **will not be granted** in situations where the proposed discussion requires consideration of new claim limitations which had not been previously presented or prosecuted; or in situations where arguments are a simple reiteration of the arguments which had been presented during prosecution (see MPEP 713.09 & 714.13).

> "Normally, one interview after final rejection is permitted. However, prior to the interview, the intended purpose and content of the interview should be presented briefly, preferably in writing. Such an interview may be granted if the examiner is convinced that disposal or clarification for appeal may be accomplished with only nominal further consideration. Interviews merely to restate arguments of record or to discuss new limitations which would require more than nominal reconsideration or new search should be denied. See MPEP § 714.13.)"

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
10/3/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK